# Table 5b. Antiplatelet Therapy: Selected Clinical Data

*Last Updated: May 31, 2022*

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for antiplatelet therapy. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

| Methods | Results | Limitations and Interpretation |
|---|---|---|
| **ACTIV-4a: Open-Label, Adaptive RCT of Adding a P2Y12 Inhibitor to Anticoagulant Therapy in Noncritically Ill Hospitalized Patients With COVID-19 in Brazil, Italy, Spain, and the United States[1]** | | |
| **Key Inclusion Criteria:**<br>• Laboratory-confirmed SARS-CoV-2 infection<br>• Any 1 of the following:<br>  • D-dimer level ≥2 times ULN<br>  • Aged 60–84 years<br>  • Aged <60 years with oxygen requirement >2 L/min, HTN, DM, eGFR <60 mL/min, CVD, or BMI ≥35<br>**Key Exclusion Criteria:**<br>• Required HFNC oxygen ≥20 L/min, NIV, MV, ECMO, vasopressors, or inotropes<br>• >72 hours since hospital admission<br>**Interventions:**<br>• Therapeutic dose of heparin plus P2Y12 inhibitor for 14 days or until discharge (n = 293)<br>• Therapeutic dose of heparin (usual care arm) (n = 269)<br>**Primary Endpoints:**<br>• Number of organ support-free days by Day 21<br>• Major bleeding event by Day 28<br>**Key Secondary Endpoint:**<br>• Major thrombotic event or death by Day 28 | **Participant Characteristics:**<br>• Mean age 53 years; 42% women; 62% White<br>• HTN: 43% in P2Y12 inhibitor arm vs. 55% in usual care arm<br>• 65% on glucocorticoids; 52% on RDV; 3% on IL-6 inhibitors; 14% on aspirin<br>• Median duration of P2Y12 inhibitor treatment: 6 days<br>  • 63% received ticagrelor; 37% received clopidogrel<br>**Primary Outcomes:**<br>• Median number of organ support-free days: 21 in both arms (aOR 0.83; 95% CrI, 0.55–1.25; posterior probability of futility 96%)<br>• Major bleeding events: 6 patients (2.0%) in P2Y12 inhibitor arm vs. 2 (0.7%) in usual care arm (aOR 3.31; 95% CI, 0.64–17.2; *P* = 0.15)<br>**Secondary Outcome:**<br>• Major thrombotic event or death by Day 28: 6.1% in P2Y12 inhibitor arm vs. 4.5% in usual care arm (aOR 1.42; 95% CI, 0.64–3.13) | **Key Limitations:**<br>• Open-label study<br>• Study stopped early for futility<br>• Different P2Y12 inhibitors used<br>• Median duration of P2Y12 inhibitor use was 6 days, which may not be sufficient to observe effects.<br>**Interpretation:**<br>• Among hospitalized patients with COVID-19 who were not critically ill, adding a P2Y12 inhibitor to a therapeutic dose of heparin did not increase the number of organ support-free days.<br>• Major bleeding events occurred infrequently during the study. The number of patients who experienced a major bleeding event was not significantly different between the arms. |

| Methods | Results | Limitations and Interpretation |
|---|---|---|
| **RECOVERY: Open-Label RCT of Aspirin in Hospitalized Patients With COVID-19 in Indonesia, Nepal, and the United Kingdom[2]** | | |
| **Key Inclusion Criterion:**<br>• Clinically suspected or laboratory-confirmed SARS-CoV-2 infection<br>**Key Exclusion Criteria:**<br>• Hypersensitivity to aspirin<br>• Recent history of major bleeding events<br>• Currently receiving aspirin or another antiplatelet treatment<br>**Interventions:**<br>• Aspirin 150 mg once daily until discharge (n = 7,351)<br>• SOC alone (n = 7,541)<br>**Primary Endpoint:**<br>• All-cause mortality at 28 days<br>**Key Secondary Endpoints:**<br>• Progression to MV or death at 28 days<br>• Major bleeding or thrombotic events at 28 days | **Participant Characteristics:**<br>• Mean age 59 years; 62% men; 75% White<br>• 97% had laboratory-confirmed SARS-CoV-2 infection<br>• At baseline:<br>  • 33% on NIV or MV<br>  • 34% on intermediate- or therapeutic-dose LMWH<br>  • 60% on standard-dose LMWH<br>  • 7% received no thromboprophylaxis<br>  • 94% on corticosteroids; 26% on RDV; 13% on tocilizumab; 6% on baricitinib<br>**Primary Outcome:**<br>• All-cause mortality at 28 days: 17% in both arms (rate ratio 0.96; 95% CI, 0.89–1.04; *P* = 0.35)<br>**Secondary Outcomes:**<br>• Progression to MV or death at 28 days: 21% in aspirin arm vs. 22% in SOC arm (risk ratio 0.96; 95% CI, 0.90–1.03)<br>• Major bleeding events at 28 days: 1.6% in aspirin arm vs. 1.0% in SOC arm (*P* = 0.0028)<br>• Thrombotic events: 4.6% in aspirin arm vs. 5.3% in SOC arm (*P* = 0.07) | **Key Limitation:**<br>• Because of open-label design, reporting of thrombotic and major bleeding events may have influenced treatment allocation.<br>**Interpretation:**<br>• In hospitalized patients with COVID-19, the use of aspirin was not associated with reductions in 28-day mortality or the risk of progressing to MV or death. |

| Methods | Results | Limitations and Interpretation |
|---|---|---|
| **REMAP-CAP: Open-Label, Adaptive RCT of Antiplatelet Therapy in Critically Ill Patients With COVID-19 in 8 Countries in Europe and Asia[3]** | | |
| **Key Inclusion Criteria:**<br>• Clinically suspected or laboratory-confirmed SARS-CoV-2 infection<br>• Within 48 hours of ICU admission<br>**Key Exclusion Criteria:**<br>• Bleeding risk sufficient to contraindicate antiplatelet therapy<br>• CrCl <30 mL/min<br>• Receiving antiplatelet therapy or NSAID<br>**Interventions:**<br>• 1 of the following plus anticoagulation for 14 days or until hospital discharge, whichever came first:<br>  • Aspirin 75–100 mg once daily (n = 565)<br>  • P2Y12 inhibitor (n = 455)<br>  • No antiplatelet therapy (control arm) (n = 529)<br>**Primary Endpoint:**<br>• Number of organ support-free days by Day 21<br>**Key Secondary Endpoints:**<br>• Survival to hospital discharge<br>• Survival to Day 90<br>• Major bleeding event by Day 14 | **Participant Characteristics:**<br>• Mean age 57 years; 34% women; 77% White<br>• At baseline, 98% on LMWH:<br>  • 19% on low-dose LMWH<br>  • 59% on intermediate-dose LMWH<br>  • 12% therapeutic-dose LMWH<br>• 98% on steroids; 21% on RDV; 44% on tocilizumab; 11% on sarilumab<br>• In P2Y12 inhibitor arm, 88.5% received clopidogrel, 1.3% received ticagrelor, 1.3% received prasugrel, and 8.8% received an unknown P2Y12 inhibitor<br>**Primary Outcome:**<br>• Data from aspirin and P2Y12 inhibitor arms were pooled and reported as "pooled antiplatelet arm" in final analysis:<br>  • Median number of organ support-free days: 7 in pooled antiplatelet arm and control arm (aOR 1.02; 95% CrI, 0.86–1.23; posterior probability of futility 96%)<br>**Secondary Outcomes:**<br>• Survival to hospital discharge: 71.5% in pooled antiplatelet arm vs. 67.9% in control arm (median-adjusted OR 1.27; 95% CrI, 0.99–1.62; adjusted absolute difference 5%; 95% CrI, -0.2% to 9.5%; 97% posterior probability of efficacy)<br>• Survival to Day 90: 72% in pooled antiplatelet arm vs. 68% in control arm (HR with pooled antiplatelets 1.22; 95% CrI, 1.06–1.40; 99.7% posterior probability of efficacy)<br>• Major bleeding event by Day 14: 21 (2.1%) in pooled antiplatelet arm vs. 2 (0.4%) in control arm (aOR 2.97; 95% CrI, 1.23–8.28; posterior probability of harm 99.4%) | **Key Limitations:**<br>• Open-label study<br>• Different P2Y12 inhibitors used<br>• Trial stopped for futility. Because equivalence for aspirin and P2Y12 inhibitor arms was reached, these arms were pooled for analyses.<br>**Interpretation:**<br>• In critically ill patients with COVID-19, the use of aspirin or a P2Y12 inhibitor did not reduce the number of organ support-free days or in-hospital mortality.<br>• Patients in pooled antiplatelet arm had more major bleeding events than those in the control arm, but they had improved survival over 90 days. |

**Key:** BMI = body mass index; CrCl = creatinine clearance; CVD = cardiovascular disease; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HFNC = high-flow nasal cannula; HTN = hypertension; ICU = intensive care unit; IL = interleukin; LMWH = low-molecular-weight heparin; MV = mechanical ventilation; NIV = noninvasive ventilation; NSAID = nonsteroidal anti-inflammatory drug; the Panel = the COVID-19 Treatment Guidelines Panel; RCT = randomized controlled trial; RDV = remdesivir; SOC = standard of care; ULN = upper limit of normal

## References


1. Berger JS, Kornblith LZ, Gong MN, et al. Effect of P2Y12 inhibitors on survival free of organ support among non-critically ill hospitalized patients with COVID-19: a randomized clinical trial. *JAMA*. 2022;327(3):227-236. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35040887.
2. RECOVERY Collaborative Group. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2022;399(10320):143-151. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34800427.
3. REMAP-CAP Writing Committee for the REMAP-CAP Investigators, Bradbury CA, Lawler PR, et al. Effect of antiplatelet therapy on survival and organ support-free days in critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2022;327(13):1247-1259. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35315874.